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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/526,372	OHIZUMI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/29/08 and 9/29/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 13-25* is/are pending in the application.

4a) Of the above claim(s) *15,17,22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13,14,16,18-21,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/29/08 has been entered.

2. Claims 1-9 and 13-25 are pending.

3. Applicant's election of MRL/lpr (Fas mutation/SLE) mouse and systemic erythematosous as the species filed on 9/29/08, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 15 (Fas ligand), 17, 22 (Fas ligand) and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

5. Claims 1-9, 13-14, 16, 18-21, 23 and 25 are under examination in the instant application.

6. Applicant's IDS, filed 11/13/07, is acknowledged.

7. Claim 13, 13, and 23 are objected to because the "erythematodes" is not English word, the English translation for erythematodes is erythematosous.

8. Claim 13 is objected to because "thyreoditis" is misspelled, the English spelling for it is thyroiditis. Further, "autoimuune" on line 1 is misspelled. The correct spelling is autoimmune. Applicant is required to check the spelling of all the autoimmune diseases in claims and specification.

9. The amendment filed 1/29/08 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment filed on 1/29/08 substitute the Sequence listing to correct a typographical error in SEQ ID NO: 6 represents a departure from the specification and the claims as originally filed. Applicant points out that SEQ ID NO: 6 recites Val-Leu-Leu at amio acid positions 10-12. This is incorrect. The correct amino acids at positions 10-12 of SEQ ID NO: 6 should be Leu-Leu-Val. Applicant points to Fig. 1 for support. However, the specification and the claims as originally filed have no support for the new replacement of SEQ ID NO:6. However, Figure 1 lists amino acids 10-12 as "LVV" not as "LLV" as amended here.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 13-14, 16, 18-21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for producing antibody against GPC-3 protein comprising immunizing MLR/lpr mouse that develops SLE with a GPC-3 protein.

Applicant is not in possession of the methods recited in claims 1-9, 1314, 16, 18-21, 23 and 25.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the nonhuman animal to be immunized or any nonhuman animal that develops autoimmune disease) to describe the claimed genus, nor does it provide a description of structural features that are common to species (human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the nonhuman animal to be immunized or any nonhuman animal that develops autoimmune disease). The specification provides no structural description of human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the nonhuman animal to be immunized or any nonhuman animal that develops autoimmune disease other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed **antigen/nonhuman animal** looks like. The specification's disclosure is inadequate to describe the claimed genus of **antigen/**.

The claims as written appear to encompass the use of any **nonhuman animal** that develops autoimmune disease and any **human antigen** that has sequence identity of 94% or more at the amino acid sequence level (which encompasses subsequences of the native protein) to homolog protein of the nonhuman animal to be immunized. Applicant has disclosed only glypican-3 protein and MLR/lpr mouse; therefore, the skilled artisan cannot envision all the contemplated human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the nonhuman animal to be immunized or any nonhuman animal that develops autoimmune disease possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description"

Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 1-9, 13-14, 16, 18-21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing antibody against GPC-3 protein comprising immunizing MLR/lpr mouse that develops SLE with a GPC-3 protein, does not reasonably provide enablement for methods recited in claims 1-9, 1314, 16, 18-21, 23 and 25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification fails to provide an enabling disclosure for producing an antibody including anti-glypican antibody) production using any nonhuman animal that develops autoimmune disease (including Fas function defects) the instant methods as claimed. Claim 13 recites 21 different autoimmune diseases. Some of these autoimmune diseases do not have a nonhuman animal model yet and the specification fails to show that any nonhuman animal model can be used in the production of antibody against non-self antigens. A nonhuman mammal showing a phenotype of an autoimmune disease is unpredictable. Creating transgenic/knockout nonhuman mammals across board, without evidence to the contrary, transgene expression and knockout

phenotype in different species of transgenic animals is not consistent and varies according to the particular host species. The observation is supported by Mullins et al (J. Clin. Invest. 1996, 97:1557-1560) and Linder (Lab Animal 2001, 30:34-39. Mullins et al teaches that a given construct may react very differently from one species to another (page 1559, Summary). Linder teaches that the genetic background and the surrounding environment are often overlooked parameters that can significantly affect the observed phonotype. Other factors include mutations that are actually hypomorphs (i.e., mutations that cause only a partial decrease in gene expression) rather than null alleles; compensatory pathways, and transgeness-specific factors, including site of integration, transgene copy number, and insertional mutations. Genetic background is defined as a collection of all genes present in an organism that influence a trait or traits. While most of the commonly used inbred strains share a fairly common origin, each strain has its own unique set of characeristics or background lesions. The phenotype of mice carrying a modified gene will vary depending on the genetic background because of the presence of genetic modifiers (Allelic variants at loci other than the one being genetically modified) in the inbred strain genome (see entire article). Accordingly, the phenotypes resulting from targeted disruption of an antigenic gene in different strains are expected to be varied and unpredictable.

Logan and Sharma (Clin Exp Pharmacol Physiol. 1999 Dec;26(12):1020-5) teach that that the challenge in the development of transgenic animals is not in this process, but in the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level. Problems with obtaining expression of transgenes in animals have been related to the inability to routinely obtain high levels of expression, especially over multiple generations, and the observation of variegated expression, whereby not all cells in an organ will express the gene (page 1021, under PRODUCTION OF TRANSGENIC PIGS). Thus, the phenotypes resulting from homozygous knock out of a particular antigen are expected to be varied and unpredictable. The skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout for particular gene.

The resulting genotype and phenotype of the nonhuman animal that develops autoimmune disease including Fas function defects vary significantly depending on the genes being manipulated, and the animals being used because gene manipulation and the resulting phenotype of transgenic animals is not always consistent due to reasons such as gene functional redundancy and species difference, and that homozygous transgenic animal may not be viable. Pearson (Nature 2002;415:8-9) comments, " Indeed, clear and consistent phenotypes now seem to be the exception rather than the rule. " (left column, page 8). Accordingly, the phenotypes resulting from homozygous knock out of a particular antigen are expected to be varied and unpredictable. The skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout for any particular gene encoding an auto-antigen.

In general, antibodies will not be raised against self-antigens nor against highly conserved domains of proteins that do not vary between species. However, Declerck et al (J Biol Chem. 1995 Apr 14;270(15):8397-400) reported the generation of monoclonal antibodies against autologous proteins in gene-inactivated mice. Declerck et al teach that the preparation of anti-

urine tissue-type plasminogen activator (t-PA) in a KO mouse, wherein the mouse lacked a functional t-PA gene. Declerck et al suggested that this approach could be applied to other classes of proteins allowing the generation of monoclonal antibodies against conserved epitopes, which could not be raised in wild-type animals because of their "self-antigen" nature (see abstract). However, the art does not recognized immunizing any KO mouse that develops any autoimmune disease with any human native protein (heterologous) which has high sequence identity to homolog protein of the non-human animal. Autoantigens are normal constituents of the body, which remain typically are not recognized by the immune system. Given that the KO mice do not produce autoantibodies to all their autologous proteins (autoantigens), it cannot be seen how such KO mice would produce antibodies to proteins that have 100% homology to protein of the non-human animal to be immunized because these proteins are considered as auoantigens.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 7-9, 14, 16, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No. 6,235,714.

The `714 patent teaches six MRL/lpr mice were hyperimmunized with target antigen such as EGFR, TNFα, IL-1β among others (see fig. 19 and col., 8, under selection and preparation of CRAAs in particular) to drive the immune system to generate catalytic antibodies. Blood will be obtained from the retro-orbital plexus at ten day intervals (see col., 14, under immunization, col., 43, lines 56-66 in particular). Claims 10-12 are included because the target antigens listed in fig. 19, the antigen protein exhibits high amino acid sequence homology in a human and mouse, wherein the amino acid sequence homology 94 % or higher in the absence of evidence to the contrary. The `714 patent further teaches that the MRL/lpr mouse strain, contain a mutation of the Fas apoptosis gene is believed to permit proliferation of T and B cells and expression of lupus-like disease (see col. 36, lines 63-65). The `714 patent teaches that the human antigen in the exemplary CRAA-IL1-β peptide (PKKKMEK) (see fig. 16) shares a native protein which has PKKKMEK sequence identity of 100% at the amino acid sequence level to the mouse protein antigen (see Exhibit A, under amino acid positions in the "Query" 90-97 provided in the previous Office Action). Further, the `714 patent teaches other target antigens listed in fig. 19 such as Macrophage inhibitory factor, C5, GPIIb/IIIa receptor (96% at the amino acid level), FVII, IL-4, IL-5, IgE, Eotaxin, PDGF, αvβ3 integrin (96% at the amino acid level). Applicant fail to address

the homology of said antigens. These antigen protein exhibits high amino acid sequence homology in a human and mouse, wherein the native protein has a sequence identity more than 94% at the "amino acid sequence level" to a homolog protein of the nonhuman animal to be immunized in the absence of evidence to the contrary

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 1/29/08, have been fully considered, but have not been found convincing.

Applicant argues that claim 7 as amended is directed to only those native proteins having an amino acid sequence identity of 94% or greater.

However, Paul et al teaches that the human antigen in the exemplary CRAA-IL1-β peptide (PKKKMEK) (see fig. 16) shares a native protein which has PKKKMEK sequence identity of 100% at the "amino acid sequence level" to the mouse protein antigen. Given that the claim does not specify the length of the amino acid level the PKKKMEK reads on the claimed invention.

Applicant argues that Paul et al. disclose at lines 26 to 35 in the 3rd column, that the CRAA have three essential elements and have the following formula:X1-Y-E-X2. X1 and X2 are peptide sequences containing about 3-10 contiguous amino acids forming an epitope of a target antigen. Y is a basic residue (Arg or Lys). E is an electrophilic reaction center designed to react covalently with nucleophilic side chains of certain amino acids. That is, the invention disclosed in Paul et al. has as an essential feature the requirement that E must be present adjacent to Y in order to obtain antibodies.

However, the term "has" base claim 7 is open-ended. It would open up the claim to include the additional amino acids recited in PKKKMEK antigen.

Applicant submits that a soluble protein is used to immunize a nonhuman animal. That is, a protein which is expressed on a membrane of a cell is solubilized to be used, as Examples of the present application describe, and a protein which is secreted as a soluble form can be used as it because it is already soluble. Applicant submits that in Paul et al., a mouse is immunized with an antigen expressing cell as disclosed in column 14. That is, the method of Paul et al. can be applied for only insoluble antigens.

It is not clear to the examiner as how the issue of "the solublization of the protein issue" is relevant to the instant rejection. Further, Applicant is arguing limitations not present in the instant claims. In addition, the `714 patent teaches that polypeptides to be targeted include soluble ligands and the membrane bound receptors for these ligands. Further injections with the soluble extracellular domain of the epidermal growth factor receptor (exEGFR) (25 μg) will be administered. To drive the immune system to generate catalytic antibodies, six MRL/lpr mice will be hyperimmunized i.p. with the TSA-EGFR conjugated to keyhole limpet hemocyanin

(KLH) (50 μg protein) in RIBI according to the above scheme (see col. 14). Accordingly, Paul et al uses soluble antigens.

Regarding the proteins listed in Figs 19A and 19B of Paul et al., macrophage inhibitory factor, TNFa, Complement Component C5, IL-Iβ, clotting factor VII, IL-4, IL-5, IgE, eotaxin and PDGF are liquid (soluble) factors. As to these liquid factors, it is impossible to produce an antibody since these liquid factors are secreted in a culture medium and are not bound to the surface of a cell. Accordingly, these liquid factors are not disclosed in Paul et al. such that an antibody can be produced. That is, Paul et al. does not provide an enabling disclosure of the presently claimed invention.

It is the examiner's position Paul's patent teaches producing an antibody comprising immunizing a nonhuman animal with Fas function defect with a human native protein which has a sequence identity of 94% or more at the amino acid sequence level to homolog protein of the nonhuman animal to be immunized. It is unclear to the examiner as why it is impossible to produce an antibody to TNFa, Complement Component C5, IL-Iβ, clotting factor VII, IL-4, IL-5, IgE, eotaxin and PDGF. The prior art teach antibodies to all these secreted protein. Further, if it is impossible to produce antibodies to secreted protein, then Applicant's specification also is not enabled for all native protein which has a sequence identify of 94% or more at the amino acid sequence level to homolog protein of the nonhuman animal to be immunized because by Applicant's admission that antibodies to secreted proteins (subgenus) which fall in the claimed genus (native protein) are impossible to make.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-4, 6, 13, 20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Lage et al (2001, IDS CA).

The `390 publication teaches that a mouse having an autoimmune disease such as MRL/I mouse can be used to produce a monoclonal antibody (see the English translation provided by

Applicant). The `390 publication teaches a method of producing a hybridoma which produces the monoclonal antibody, wherein an animal having an autoimmune disease is used as a mammal from which plasma cells are obtained. It is preferable that the animal is selected considering the adaptability to myeloma used for cell fusion. A mouse or rat is preferable, wherein the mouse having an autoimmune disease includes N2B, NZW, B/WF1, MRL/I, BXSB male and SLN1 strain. A rat having an autoimmune disease includes a rat in which hypertension occurs spontaneously. Further, a normal mouse such as Balb/c of which the ability to produce autoantibodies increases by being administered with a polyclonal B cells activator such as lipopolysaccharide (LPS) of a gram negative bacterium and dextran sulfate and which is in the state of autoimmune disease may be used (see the Partial English translation of Japanese Publication No. 0104739).

The `198 patent teaches a preparation containing immunogens is used to immunize animals. Thereupon, the immunized animals are preferred to be selected with consideration of their compatibility with the myeloma used in cell fusion. Mice or rats are preferable. When using glycolipids which contain N-glycolylneuraminic acid, an object of this invention, animals with autoimmune disease are more preferable and mice with autoimmune disease are the most preferable. As the mice with autoimmune disease, there are NZB, NZW, B/WF1, MRL/l, BXSB (SLE) male, SL/Ni and other mice available. Normal mice such as Balb/c may be used as immunized animals if the mice become autoimmune by raising their autoantibody producing ability caused by the injection of a polyclonal B cell activator (PBA) such as bacterial lipopoly-saccharide (LPS) or dexstran sulfate (col. 8, lines 37-53 and claim 12 in particular). The `198 patent teaches that the glycolipids which contain N-glycolylneuraminic acid including gangliosides with the H-D antigen activity, one of the objects in this invention, are known to exist widely in mouse tissues, so that these glycolipids are autoantigens for mice. Therefore, these glycolipids are thought to have extremely weak immunogenicity. It is very difficult to obtain the monoclonal antibody specific to or against glycolipids containing N-glycolylneuraminic acid according to the conventional methods which use normal mice such as Balb/c mice as immunized animals. On the other hand, it is known that mice with autoimmune disease produce antibodies against autoantigens such as anti-nuclear antibodies or anti-erythrocyte antibodies (see col., 8, last ¶). The `198 patent teaches that the produced antibodies are very effective for study of cancer's occurrence mechanism diagnosis and treatment (see abstract in particular).

The claimed invention differs from the reference teachings only by the recitation that the antigen is glypican in claim 1 such as glypican-3 in claim 6.

Lage et al teach that proteoglycans are glycoproteins containing various sulfated glycosaminoglycan residues, e.g., heparan sulfate. These glycoproteins, designated as heparan sulfate proteoglycans (HSPGs), are widely distributed in many tissues, occurring in various forms of extracellular matrices, at cell surfaces, and in intracellular granules. HS is a regulatory polysaccharide. Glypicans, also called glypican-related integral membrane proteoglycans (GRIPS), are one of two major families of transmembrane HSPGs. The glypicans are anchored to membranes by a glycosyl-phosphatidylinositol (GPI) anchor. This covalently attached GPI

residue was the source of the term glypican, which is derived from glycosylphosphatidylinositol-anchored proteoglycan (see page 438, under Introduction). Lage et al teach that despite many efforts, no mAb specifically recognizing the GPC3 polypeptide could be generated, it appears obvious that GPC3 is only weakly or not immunogenic in mice.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb against GPC3 using autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390 publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 3-9, 14, 16, 18-19, 21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Lage et al (2001, IDS CA) as applied to claims 1-4, 6, 13, 20 and 23 above and further in view of U.S. Pat. No. 5,641,488.

The teachings of the `390 publication and the `198 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the nonhuman animal that develops the autoimmune disease is MRL/lpr.

The `488 patent teaches methods for producing an antibody which specifically binds to a chosen antigen using the so-called autoreactive animals, such as mouse strains NZBXSWR(F1) and MRL lpr/lpr (SLE model) animals may be used. "Autoreactive" animals do not require treatment to undergo B cell hypermutation. Such animals need only be immunized with the immunogen of choice when they are in an autoreactive state. Determination of when the animal is in such a state is easily determined by one skilled in the art (see col. 17, lines 23-30).

Claim 7 is included because GPC3 has 94% sequence identity with the mouse.

Claims 14, 16, 18, 21, 23 and 25 are included because the recited limitations are inherent properties of the MRL/lpr mouse.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use MRL lpr/lpr taught by the `488 patent in a method for producing an antibody to GPC3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such animals need only be immunized with the immunogen of choice when they are in an autoreactive state.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/29/08, have been fully considered, but have not been found convincing.

Applicant's submission of verified English language translation of the priority document PCT/JP02/08998, filed 7/17/07 is sufficient to predates the publication date of Fu et al (9/20/02).

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 2, 2008

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